

SUPPORT FOR THE AMENDMENT

The claims are amended in a non-narrowing manner only to remove brackets and parentheses, as well as place the claims in proper form. Claims 10-12 have been canceled in favor of new Claims 13-24. Therefore, support for the newly added claims is found in the original claims and throughout the specification. No new matter is believed to be introduced by the amendment.

REMARKS

Claim 1 is amended. Claims 10-12 are cancelled in favor of new Claims 13-24. Claims 1-9 and 13-24 are pending. Favorable reconsideration is respectfully requested.

At the outset, Applicants thank Examiner Anderson for indicating that the amendment would further favorable prosecution of the present application and for helpful comments during the discussion held on October 21, 2002, and in the Office Action for overcoming the rejections. Finally, Applicants thank the Examiner for indicating that Claims 3, 4, 7, and 8 are allowable.

The rejection of Claims 1-2, 5-6 and 9-12 under 35 U.S.C. § 103(a) over US 5,223,522 (US'522), WO 97/32863 (WO'863), and EP 0 846 693 (EP'693) or in any combination is traversed below.

At best, US'522 discloses a benzylthiazolidine-2,4-dione. However, US'522 fails to disclose that the benzylthiazolidine-2,4-dione contains a methoxy substituent at a site equivalent to R3 in formula (I) in Claim 1.

At best, WO'863 discloses a benzylthiazolidine-2,4-dione. However, WO'863 fails to disclose that the benzylthiazolidine-2,4-dione contains a methoxy substituent at a site equivalent to R3 in formula (I) in Claim 1.

At best, EP'693 discloses a benzylthiazolidione compounds. However, EP'693 fails to disclose that the benzylthiazolidione compound contains a CH₂NHCO at a site equivalent to A in formula (I) in Claim 1.

The claimed invention relates, in part, to benzylthiazolidine-2,4-dione derivatives that may contain a methoxy substituent as R3 in formula (I) (see Claim 1 above). Further, the claimed compounds may contain a CH₂NHCO at the position A.

The Office contends it would be obvious to obtain the claimed compounds by substituting the benzylthiazolidine-2,4-dione compounds disclosed in US'522 and/or WO'863 with the methoxy substituents disclosed in EP'693. Motivation to modify the disclosure of one reference must be expressly found in the disclosures of the cited references themselves or well within the knowledge of the skilled artisan. The Office contends that this motivation is "to create other useful the benzylthiazolidine-2,4-dione compounds useful as blood glucose lowering drugs". The Office does not provide references demonstrating that the skilled artisan would have known to make a benzylthiazolidine-2,4-dione compound containing a methoxy as R3 and CH₂NHCO as A in formula (I). In fact, the Office merely states a conclusion absent any evidence. Further, there is not one disclosure found in any of the cited references suggesting that it would be desirable to modify a benzylthiazolidine-2,4-dione compound contain a methoxy as R3 and CH₂NHCO as A in formula (I). Of course, the skilled artisan may wish to find additional benzylthiazolidine-2,4-dione compounds useful as blood glucose-lowering drugs. In fact, any compound useful as blood glucose-lowering drug are desirable. The key is that there is no guide found in

any one of the references to modify there disclosures in a specific manner to obtain the claimed compounds. Further, the Office is reminded that it is not permitted to use the present specification as a guidepost to combine the disparate disclosures of the cited references (see *In re Vaeck* 20 USPQ 2d 1438).

In light of the above, none of the references disclose or suggest the claimed compounds. Further, there is no motivation found in any of the references to modify the disclosures therein to obtain the claimed compounds. Accordingly, no *prima facie* case of obviousness can possibly exist; and therefore, withdrawal of these grounds of rejection is respectfully requested.

In arguendo, if the Office maintains that a *prima facie* case of obviousness does exist, Applicants respectfully submit that none of the references provide sufficient specificity in the disclosures therein to obtain the claimed compounds. Further, one reading these disclosures would not have expected the surprisingly superior results of the claimed compounds. The Applicants provide herewith, Exhibit A, which is a set of experiments comparing the efficacy of compounds 17, 22, 23, and 28 disclosed by EP'693 with compounds 6, 11, 15, and 22 embodied by the claimed invention in their abilities to exhibit lipid-lowering action based upon their agonist activities on PPAR (human peroxisome proliferator-activated receptor) alpha and their blood sugar-lowering action based on their agonist activity on PPAR gamma.

The Office is reminded that the Examiner suggested that such a comparative data study be submitted in support of the patentability of the claimed invention. At the above-mentioned Interview, the Examiner specifically requested comparative data provided for the above compounds. It should be noted that the Examiner also requested comparative data for compound 38 of EP'693. However, the study could

not be performed because the stock amount of this compound was too small to perform such experiments.

As an overview, the data in Exhibit A clearly demonstrate that the claimed compounds are superior in their dual agonist activity on PPAR alpha and gamma. In Table 3 of the present specification (reproduced as Table A in Exhibit A), it is clearly demonstrated that the claimed compounds show strong transactivation to both PPAR alpha and gamma. The same experimental conditions were used test the transactivation activities of the compounds 17, 22, 23, and 28 disclosed by EP'693 (see Table B in Exhibit B). The data of Table B demonstrates that, although compounds 17, 22, 23, and 28 disclosed by EP'693 are capable of activating PPAR gamma, they can not activate PPAR alpha even at concentrations as high as 10 $\mu\text{mol/L}$.

In direct contrast to the compounds disclosed by EP'693, the claimed compounds are capable of activating PPAR alpha quite readily. Further, the claimed compounds are capable of strongly activating PPAR gamma. Therefore, the claimed compounds are clearly superior in their surprising dual agonist capabilities with regards to PPAR alpha and gamma compared to the compounds disclosed by EP'693. Accordingly, the claimed compound may have both lipid-lowering and blood glucose-lowering capabilities, while those disclosed by EP'693 can not.

In light of the above discussion and Exhibit A attached hereto, it is clear that none of the cited references provide sufficient specificity to make the claimed compounds. Further, Applicants have provided data in Exhibit A (as requested by the Examiner) which clearly demonstrates the surprisingly superior qualities of the claimed compounds (e.g. dual agonist activating activity of PPAR alpha and gamma).

The rejection of Claims 1 and 10-12 under 35 U.S.C. § 112, second paragraph, is obviated by the cancellation of Claims 10-12. The Office's attention is drawn to new Claims 13-24 which are not duplicates of Claim 1 where the method claims contain a positive active step. Further, Claim 1 is amended to remove the parentheses. Accordingly, withdrawal of this ground of objection is respectfully requested.

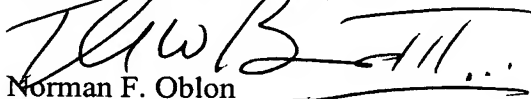
The objection to Claims 10-12 is obviated by the cancellation of these claims. The Office's attention is drawn to new Claims 13-24 which are not duplicates of Claim 1 where the method claims contain a positive active step. Accordingly, withdrawal of this ground of objection is respectfully requested.

Applicants respectfully submit that the present application is now in condition for allowance. Favorable reconsideration is respectfully requested. Should anything

further be required to place this application in condition for allowance, the Examiner is requested to contact Applicants' Attorney by telephone.

Respectfully submitted,

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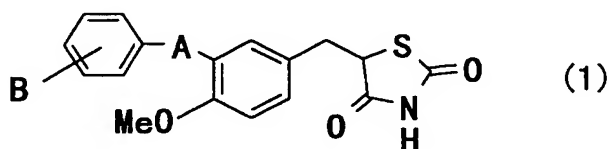
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Amendment Filed on:
HEREWITH

IN THE CLAIMS

Please amend the claims as follows.

--Claims 10-12 are canceled.--

--1. (Amended) A [Substituted] substituted benzylthiazolidine-2,4-dione
[derivatives] derivative represented by a general formula (1)



[[] wherein the bond mode of A denotes -CH₂CONH-, -NHCONH-, -CH₂CH₂CO- or -NHCOCH₂-, and B denotes a lower alkyl group with carbon atoms of 1 to 4, lower alkoxy group with carbon atoms of 1 to 3, halogen atom, trifluoromethyl group, trifluoro-methoxy group, phenyl group which is unsubstituted or may have substituents, phenoxy group which is unsubstituted or may have substituents or benzyloxy group which is unsubstituted or may have substituents[[]], their medicinally acceptable salts and their hydrates.--

--Claims 13-24 are added.--

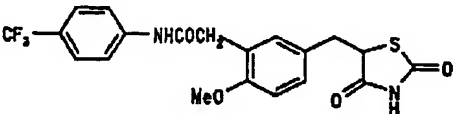
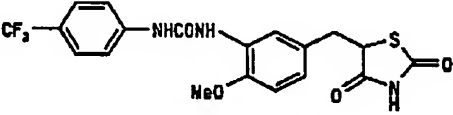
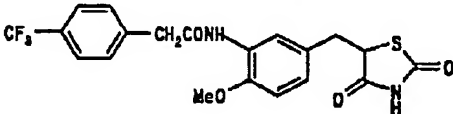
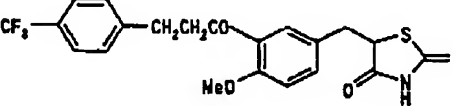
- 2) The comparative experimental data, which are requested by the Examiner, have been prepared as described under.

The present invention submits the compound having agonist activity of human peroxisome proliferator-activated receptor (PPAR) and has been developed on the expectation of exhibiting lipid-lowering action based on agonist activity of PPAR alpha in addition of blood sugar-lowering action

based on agonist activity of PPAR gamma. That is, the present invention has developed a dual agonist capable of activating PPAR alpha and gamma.

In Table 3 of the present specification, it is described that the Example compounds of the present invention show the strong transactivation to the both of PPAR alpha and gamma. The data of transactivation of the present compound are transferred from the specification as under.

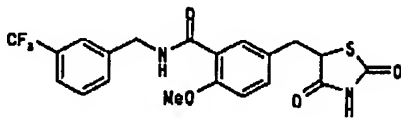
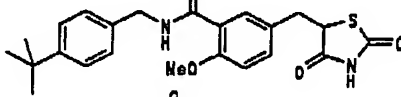
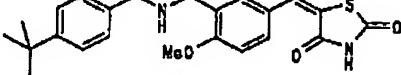
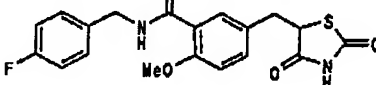
(Table A) Transactivation of the present compound

Example No.	Structure	Transactivation	
		PPAR α	PPAR γ
		EC ₅₀ (μ mol/L)	EC ₅₀ (μ mol/L)
6		0. 60	3. 30
11		0. 55	0. 43
15		0. 86	1. 10
22		0. 80	0. 40

From this result, it is demonstrated that the compounds represented by bonding modes of four kinds defined for A in the general formula (1) of the present invention have the activation action to PPAR alpha and gamma.

Next, the tested result of the transactivation by the same experiment concerning Examples 17, 22, 23, 28 of the cited reference EP 0 846 693 is shown below (the data of Example 38 is also requested, but the data thereof could not be derived, because the amount of said sample was too small therefor).

(Table B) Transactivation of the cited reference compounds

Example No.	Structure	Transactivation	
		PPAR α	PPAR γ
		EC ₅₀ (μ mol/L)	EC ₅₀ (μ mol/L)
17		>10	0.18
22		>10	0.23
23		>10	0.50
28		>10	0.20

As this result, the cited reference compounds, although strong in activation to PPAR gamma, are considered to be very weak in activation to PPAR alpha, because it is not recognized in the level of 10 micro-mol/L. The cited reference compounds are mainly the agonist of PPAR gamma.

On the other hand, it is obvious that the present invention compounds significantly have the activation to PPAR alpha at the same time in addition of the activation to PPAR gamma. The present invention compounds are the dual agonist having activating the both of PPAR alpha and gamma.

Accordingly, the present invention compounds are expected to exhibit lipid-lowering action based on PPAR alpha together with blood sugar-lowering action based on PPAR gamma.

3) Our comment

The present invention concerns the compound having agonist activity of human peroxisome proliferator-activated receptor (PPAR) and has developed a dual agonist which can activate PPAR alpha and gamma with expecting the manifestation of lipid-lowering action based on PPAR alpha agonist together with blood sugar-lowering action based on PPAR

gamma agonist.

Comparing the PPAR activation data of the cited reference with the activation data of the present invention, we can demonstrate the existence or the non-existence of PPAR alpha activity.

The present invention compounds which are strong in activating both of PPAR alpha and gamma are expected to exhibit the effect on the aspect of lowering function of lipid, which have the excellent characteristics in comparison with the cited reference compounds.